

AWARD NUMBER: W81XWH-18-1-0602

TITLE: Optimizing Patient-Reported and Vascular Outcome Measures in Systemic Sclerosis-Associated Raynaud Phenomenon

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CONTRACTING ORGANIZATION: THE UNIVERSITY OF PITTSBURGH
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14. ABSTRACT In patient surveys, Raynaud Phenomenon (RP) is the highest-ranked disease-specific symptom affecting patient quality of life. Many promising vasoactive classes of drugs have been evaluated for RP, but none have received FDA approval for this indication. This project is designed to address four critical knowledge gaps that may influence clinical trial design: 1) What is the soundest approach to measure RP attack frequency/severity? Is the paper diary or a new smart phone application more functional and preferred? 2) What should be used as the patient-reported outcome (PRO)? 3) What is the magnitude of the effect of seasonal change on RP activity and severity? 4) What is the best provocation test to study vascular reactivity in early phase and proof-of-concept RP trials? We will use a prospective, observational cohort study design of 160 SSc-RP patients followed every 3 months over one year to accomplish all Specific Aims. Simultaneously, we will recruit 500 patients for a cross-sectional questionnaire study so that we may perform item response theory analysis and validation of the new ASRAP PRO.						
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1. **INTRODUCTION:** *Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.*

This project is to address critical knowledge gaps in clinical trial design and outcome measures for systemic-sclerosis Raynaud phenomenon (SSc-RP). These knowledge gaps include the following: 1) Does a new smart phone application perform as well as paper diaries to quantify SSc-RP frequency and duration? Is the smart phone or paper diary preferred? 2) Is our new PRO, entitled the Assessment of Scleroderma-associated RAynaud Phenomenon (ASRAP) reliable and valid? Does it perform as well or better than the current expert-derived PRO? 3) Which provocation test (cold challenge vs ischemia) provides informative data with vascular imaging in SSc-RP when compared to RP severity PROs and RP attack frequencies? 4) What is the seasonal effect (variability) on the above SSc-RP outcome measures.

2. **KEYWORDS:** *Provide a brief list of keywords (limit to 20 words).*

systemic sclerosis; Raynaud phenomenon; outcome measures; patient-reported outcome measures (PRO); endothelial function; vascular imaging; cold-challenge; post-occlusive reactive hyperemia, observational cohort study

3. **ACCOMPLISHMENTS:** *The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction.*

What were the major goals of the project?

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

The overarching goal of this project is to improve clinical trials in SSc-RP by developing and validating patient-derived PROs phase 2/3 trials, and discerning the optimal type of provocation test and vascular imaging for proof-of-concept trials. Through a three center, one-year observational cohort study we are attaining the effect size of seasonal variability on all of the above studies. Embedded within this cohort study we are developing and testing a new smart phone application to report in real-time SSc-RP attacks and obtaining GPS-accurate temperature at the time of attack, as well as evaluating construct validity of our new SSc-RP PRO, ASRAP. Through a separate 500-person cross-sectional study we are evaluating criterion validity and item response theory reduction of the ASRAP. There are thus five specific goals:

- 1) Perform usability testing and final development of the smart phone application (**completed Spring 2019**).
- 2) Perform a cross-sectional study of 500 patients of the ASRAP and related questionnaires (**completed March 2020**). This data will permit evaluation of criterion validity and provide data for item response analysis (**ongoing**).
- 3) Compare the smart phone application on several measures compared to the traditional paper diary reporting which is currently used in clinical trials (**ongoing**).
- 4) Perform a one-year observational study of SSc-RP measures in which diaries (paper and smartphone), our new ASRAP questionnaire along with multiple PROs are collected across seasons. The goal is to assess variability produced by season to inform effect size in future clinical trials (**ongoing**).
- 5) Over the one-year of observation perform functional imaging using laser speckle contrast and infrared thermography testing two different provocation tests (cold-challenge and ischemia/reperfusion) (**ongoing**).

What was accomplished under these goals?

For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

We will present major activities, objects, results/outcomes, developments and conclusions by Goal, as the activities within each Goal are quite different.

Goal 1: *Perform usability testing and complete development of the smart phone application.*

Major activities: The primary goal was completed in Year 1 of the award, as reported in the first annual report (August 2019). Major activities since the last report have been ongoing support of the smart phone application with data acquisition. The app is consistently updated.

Specific objectives: To support and update the app to facilitate seamless data acquisition

Results/outcomes: The smart phone app has been fully developed and is operational now in our one-year observational cohort study.

Goal 2: *Perform a cross-sectional study of 500 patients to assess validity and provide data for item response analysis for the Assessment of Scleroderma Associated RAynaud's Phenomenon (ASRAP) questionnaire.*

Major activities: This was scheduled for Year 2 of the award, and originally intended to be performed at six sites (University of Pittsburgh, Johns Hopkins University (JHU), Royal National Hospital for Rheumatic Diseases (Bath), University of Utah, the Pittsburgh VA and Louisiana State University). Due to the PI leaving the institution, LSU did not participate. The goal was 500 participants. Recruitment started first for the winter Raynaud season at the University of Pittsburgh on October 15, 2019. Unfortunately, Covid-19 impacted our UK site earlier in 2020 than the US sites. Recruitment was halted due to Covid-19 at all US sites in March of 2020. In total, the University of Pittsburgh we recruited 77 subjects, JHU 54 and the University of Utah 43 prior to recruitment being paused. Simultaneously, a separately funded study was being conducted in 2019-2020 to assess the one-week reliability of the ASRAP questionnaire at three UK sites and the University of Michigan. This separate funded study was led by the co-investigator on this grant, John Pauling (Bath), and also halted early due to Covid-19. The baseline data from that study is collected exactly as in our protocol. We reviewed the study consents and approvals with our institutions and our HRPO liaison, and we are using the baseline, de-identified, data from that study to combine with our study questionnaires to complete the item response analysis for the ASRAP study, in light of the unique challenges this year. This data includes 124 questionnaires from Bath, 58 from the Royal Free Hospital Scleroderma Center in London, 56 from the University of Manchester (Salford Royal NHS Foundation Trust) and 26 from the University of Michigan. In total, this provides 438 of our original goal of 500 questionnaires. We did have a delay in completing a data use agreement between Michigan and the RNHRD. This was finally resolved in September 2020 item and that data was cleaned. It is now with Lan Yu, PhD (co-investigator) for item response theory analysis and performance of the criterion validation analysis plan.

Specific objectives since our last report: Data clean-up and start of statistical analysis. This is detailed under Major activities.

Result/outcomes: Pending the current statistical analysis

Goals 3, 4 and 5 are all encompassed within the one-year observational study. As background from prior reports, in Year 1 we developed the protocol and acquired the imaging equipment as previously reported. We had a training session at the University of Bath on all of the equipment, and had all Centers run through the planned visit. The University of Pittsburgh started recruitment in January 2020. In February 2020, our Pittsburgh research coordinator traveled to JHU and met with the team there to ensure that all equipment and study procedures were in place and running identically as at Pittsburgh. She trained the JHU coordinators on data entry so that recruitment could begin on March 1. Unfortunately, this did not occur secondary to Covid-19.

Major activities: At the University of Pittsburgh we had 6 participants begin the one-year observational trial between mid-January and mid-March when recruitment was forced to pause. For those enrolled at Pittsburgh, participants completed remote PRO questionnaires for the 3-month time-point, but vascular imaging was not obtained as face-to-face visits were not occurring in accordance with the governor's stay-at-home order. These participants did return for their 6-month visit to include vascular imaging once we were re-opened by the University. The nine-month visit is questionnaire only, and so can be completed remotely. The protocol was not altered, but we did ensure greater safety by erecting plexi-glass shields between the participant and research coordinator, an expanded cleaning protocol, and re-organizing the room so that 6-foot social distance could be maintained. We have our own, modestly sized vascular imaging room that only our Scleroderma Center staff access regularly. All personnel completed the University of Pittsburgh required Covid-19 training.

In light of the Covid-19 events, which have significantly impacted our ability to recruit patients, we are behind our proposed timeline. We have recruited and performed baseline assessments on one new additional patient since re-opening in June 2020. We have a second who is scheduled to come in for a baseline assessment. We have >20 patients at Pittsburgh who are interested in participating and have reviewed consent documents, but have deferred baseline visits until the Spring of 2021 due to concerns related to Covid-19. At Johns Hopkins their recruitment is still paused per their institution, although they have started the written procedures to be allowed to recruit, instituting similar safety mechanisms as we did in Pittsburgh. Bath has yet to be approved for study recruitment in the setting of Covid-19. This is clearly proving to be a significant challenge for us given the in-person nature of the vascular imaging. As an investigative team we have discussed this challenge at multiple team meetings and have requested effort reductions during this time period.

Specific objectives: Since the June report the objective in Pittsburgh has been to continue to follow those enrolled, and recruit for our study those patients who are comfortable returning in Pittsburgh. At Johns Hopkins the objective has been to start the re-opening process, which is ongoing. At Bath the objective has been to obtain approval to re-open. Both are delayed in the setting of Covid-19.

Results/Outcomes: We are currently in the data ascertainment phase.

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. “Training” activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. “Professional development” activities result in increased knowledge or skill in one’s area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report

How were the results disseminated to communities of interest?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report

What do you plan to do during the next reporting period to accomplish the goals?

If this is the final report, state “Nothing to Report.”

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

Goal 2: The focus in the next reporting period is completion of the item response analysis.

Goals 3/4/5: We are hoping to be able to start recruitment at Johns Hopkins and Bath by the Spring of 2021. We will continue to recruit at Pittsburgh, but are planning for intense enrollment in patients in the Spring of 2021. We have many patients who have read the consent form and are agreeable to participant, but have requested to delay until after the winter season. Most scleroderma patients have risk factors due to age, immunocompromised state or pulmonary fibrosis.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report.

What was the impact on other disciplines?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to Report

What was the impact on technology transfer?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- transfer of results to entities in government or industry;
- instances where the research has led to the initiation of a start-up company; or
- adoption of new practices.

Nothing to report.

What was the impact on society beyond science and technology?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- improving public knowledge, attitudes, skills, and abilities;
- changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or
- improving social, economic, civic, or environmental conditions.

Nothing to report.

- 5. CHANGES/PROBLEMS:** *The PD/PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency grants official whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:*

The scientific content and plan have not changed for Goals 1, 3, 4 and 5. As discussed above, for Goal 2 our cross-sectional questionnaire study was halted early due to Covid-19. We addressed this by obtaining approval to analyze additional questionnaire data from a simultaneous, complimentary ASRAP reliability study to gain the necessary power to complete the item response analysis (Goal 2).

Actual or anticipated problems or delays and actions or plans to resolve them

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Our major issue has been the halting of study procedures and recruitment secondary to Covid-19. For subjects already enrolled in the observational study continued to collect PROs and diaries at all time points, but there is missing vascular imaging from a small cohort of patients in the Spring of 2019 in accordance with the governor's stay-at-home order. With the institution of safety procedures enrolled patients did attend their late summer/early Fall vascular imaging timepoints.

What remains a challenge is potential participant hesitation to enroll during the upcoming winter months of 2020-2021 season due to Covid-19 in Pittsburgh. We have >20 additional patients who have reviewed the consent and verbally express an interest in participating, but would like to defer until the Spring of 2021 (or when a vaccine is available) as most are immunocompromised and/or have pulmonary fibrosis. We have reduced effort on funds to reflect our actual work (please see below), and are planning for an intense recruitment in the Spring of 2021. In Pittsburgh we have institutional approval to proceed with our current safety protocol. Johns Hopkins and Bath remain closed to subject enrollment at the institutional level. Johns Hopkins has submitted documents to be allowed to re-open with similar safety protocol in place. Bath is under review with their regulatory authority.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

As mentioned in our annual report in August 2019, our original expenditures were slightly higher than anticipated due to an increase in cost of our imaging equipment. No changes from anticipated expenditures occurred between August 2019 and August 2020. In August 2020 we requested an effort reduction for the University of Pittsburgh, as our staff effort is currently below the anticipated effort due to reduced recruitment in the setting of Covid-19. We expect this to increase back to anticipated effort in the Spring of 2021.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

No changes were made to the original protocol or procedures used. Small changes have been made to the physical room where the research is performed in order to ensure participant and coordinator/investigator safety. Mask-wearing is required due to the current pandemic at all sites.

Significant changes in use or care of vertebrate animals

Not applicable.

Significant changes in use of biohazards and/or select agents

Not applicable.

6. PRODUCTS: *List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state “Nothing to Report.”*

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Nothing to report, as data is currently being analyzed.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report, as data is currently being analyzed.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report

- **Website(s) or other Internet site(s)**

List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**

Identify technologies or techniques that resulted from the research activities. Describe the technologies or techniques were shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Identify inventions, patent applications with date, and/or licenses that have resulted from the research. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**

Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment and /or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:

- *data or databases;*
- *physical collections;*
- *audio or video products;*
- *software;*
- *models;*
- *educational aids or curricula;*
- *instruments or equipment;*
- *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
- *clinical interventions;*
- *new business creation; and*
- *other.*

Nothing to report for Year 2. The smart phone application was developed in Year 1.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate “no change”.

Example:

Name: Mary Smith
Project Role: Graduate Student
Researcher Identifier (e.g. ORCID ID): 1234567
Nearest person month worked: 5

Contribution to Project: Ms. Smith has performed work in the area of combined error-control and constrained coding.

Funding Support: The Ford Foundation (Complete only if the funding support is provided from other than this award.)

Name: Robyn T. Domsic, MD MPH

Project Role: Principal Investigator

Research Identifier: 0000-0002-2765-0922

Nearest person month worked: 3

Contribution to Project: Dr. Domsic serves as the project PI. She is responsible for coordinating all sites communicating with all Co-Investigators, ensuring regulatory approval is appropriate, , recruiting and retaining patients at Pittsburgh and overseeing vascular imaging. She communicates regularly with the Health Information system with respect to the smart phone application, and with Lan Yu, PhD for data clean-up and analysis.

Name: Maureen Laffoon, BS

Project Role: Coordinating Site Research Coordinator

Research Identifier not applicable

Nearest person month worked: 2

Contribution to the Project: Mrs. Laffoon is responsible for regulatory approval documents at Pittsburgh. She has trained all site research coordinators on using the RDMS database entry system as well as the smart phone application. She coordinates participant appointments and performs all vascular imaging studies at Pittsburgh. Along with Haomin Hu, she monitors the smart phone application system.

Name: Diane Koontz, BS
Project Role: Data Manager
Research Identifier not applicable
Nearest person month worked: 1
Contribution to the Project: Mrs. Koontz has managed and updated our Rheumatic Disease Management System (RDMS) which houses our observational cohort study (Goals 3, 4, 5), and performs data queries.

Name: Lan Yu, PhD
Project Role: Co-Investigator
Research Identifier 0000-0003-0680-9487
Nearest person month worked: 2
Contribution to the Project: Dr. Yu has assisted with data-clean-up for Goal 2. She is currently working on the data analysis and item response theory analysis for the ASRAP questionnaire.

Name: Haomin Hu
Project Role: Graduate student programmer
Research Identifier not applicable
Nearest person month worked: 2
Contribution to the Project: Mr. Hu manages and updates the smart phone application. He reviews the data entered at least weekly, if not daily.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Nothing to report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “Nothing to Report.”

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.

Provide the following information for each partnership:

Organization Name:

Location of Organization: (if foreign location list country)

Partner’s contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner’s facilities for project activities);*
- *Collaboration (e.g., partner’s staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

John Hopkins University Scleroderma Center

Location: Baltimore, MD

Partner’s contribution: Assisting in developing of protocol, regulatory approval, consenting of 54 patents and entering their completed questionnaires for Goal 2, training on vascular imaging/data entry for Goals 3, 4 and 5.

Royal National Hospital for Rheumatic Diseases Scleroderma Center, Royal United Hospitals

Location: Bath, UK

Partner’s contribution: Assistance in developing of protocol, regulatory approval, review of vascular imaging data.

University of Utah

Location: Salt Lake City

Partner’s contribution: Regulatory approval at Utah, consenting of 43 patents and entering their completed questionnaires for Goal 2.

VA Pittsburgh

Location: Pittsburgh, PA

Partner’s contribution: Regulatory approval for Goal 2. However, Covid-19 halted recruitment.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS:

QUAD CHARTS:

9. APPENDICES: